Endovascular Therapy in Hyperacute Ischaemic Stroke: History and Current Status

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Summary

This is a literature review on to the use of endovascular therapy in hyperacute ischaemic stroke secondary to large vessel occlusion (LVO). The prognosis for LVO is generally poor and the efficacy of intravenous tissue plasminogen activator (IV TPA) in the treatment of this subtype of stroke is questionable. It is well documented that recanalisation is associated with improved outcomes but IV TPA has limited efficacy in LVO recanalisation and the complication rates are higher for IV TPA in this stroke subset.

Improved recanalisation rates have been demonstrated with intra-arterial TPA and first and second generation mechanical techniques but the rate of favourable outcome has not overtly mirrored this improvement.

Several controversial trials using these early techniques have recently been published but fail to reflect modern practice which centres on the use of stent-retriever technology. This has been proven to be superior to older techniques. Not only are recanalisation rates higher, but the speed of recanalisation is greater and clinical results are improved.

Multiple observational studies demonstrate consistently high rates of LVO recanalisation; TICI 2b/3 in the order of 65-95% and, rates of favourable outcome (mRS 0-2) in the order of 55% (42.5-77%) in clinically moderate to severe stroke with complicating symptomatic haemorrhage in the order of 1.5-15%.

A major factor determining outcome is time to treatment but success has been demonstrated using these devices with bridging therapy, after IV TPA failure or as a stand-alone treatment.

Introduction

It is well documented that outcome in ischaemic stroke depends upon patient age, comorbidity, clinically severity, site of occlusion, thrombus load, quality of collateral circulation, time from ictus to recanalisation, degree of recanalisation and occurrence of symptomatic intracranial haemorrhage (SICH).

Up to 46% of ischaemic strokes result from large vessel occlusion (LVO) which is associated with a poor outcome with high rates of death and disability [1]. If proximal LVO is demonstrated by CT angiography (CTA), stroke patients are seven times more likely to suffer an unfavourable outcome than if no such occlusion is demonstrated [2]. LVO predicts a large infarct even if the initial infarct is small; the core infarct (non-salvageable brain tissue) expands with time, replacing the ischaemic salvageable penumbra if recanalisation is not achieved [3].

The prognosis for patients with the clinical syndrome of total anterior circulation infarction is poor; 40% die, 56% are dependent and only 4% of patients are independent [4]. For angiographically confirmed M1 and M2 middle cerebral artery (MCA) occlusions in the PROACT study control arm, 25% achieved a favourable outcome, modified Rankin scale (mRS) 0-2 and 27% died [5].

More recently, the natural history of patients with angiographically proven LVO has been specifically investigated with interim analysis of the FIRST trial, a multicentre prospective natural history study of patients presenting within eight hours, eligible for but not receiv-

ing endovascular therapy [6]. The 61 enrolled patients with National Institute of Health Stroke Scale (NIHSS)>10, median NIHSS 18 and occlusion sites of the terminal internal carotid artery (TICA) in 28% and MCA in 67% achieved a favourable 90-day outcome (mRS 0-2) in 22% and 41% died. Only 10% achieved spontaneous recanalisation. Similarly, the STOP stroke study demonstrated that in CTA proven anterior circulation occlusions, in patients with NIHSS>10, mean NIHSS 16, a favourable outcome (mRS 0-2) was achieved in only 13 of 77 patients (17%) with TICA, M1 or M2 occlusions [7]. TICA occlusions generally harbour a worse outcome [8]. When therapeutic recanalisation is not achieved in basilar artery (BA) occlusion, the outcome is poor in 98% (86% mRS 5-6) [9].

This article reviews the literature pertaining to the treatment of LVO specifically. We review the efficacy of IV TPA in this stroke subtype and highlight the impact of recanalisation and early treatment in obtaining favourable clinical outcomes.

We describe the reasoning for more effective treatment and the development of endovascular therapy (EVT). The recent trial evidence is critically appraised and a multitude of observational studies describing the use of stent-retriever technology are presented.

Recanalisation is important

A meta-analysis [10] of 53 studies encompassing 2066 patients concluded that recanalisation was associated with a four to fivefold increase in the odds of a favourable functional outcome and a four to fivefold reduction in mortality. RECANALISE [11] demonstrated a favourable outcome in 76% with recanalisation relative to 0% with no or poor recanalisation (see Table 1). In the recent IMS 3 trial [12], the proportion of patients with a mRS of 0-2 increased progressively with degree of recanalisation from 12.7% with a Thrombolysis in Cerebral Infaction (TICI) score of 0 to 71.4% with a TICI score of 3 (P<0.001).

Recanalisation and clinical outcomes with IV TPA

Intravenous (IV) TPA within 4.5 hours of ictus is currently the standard of care. IV TPA is the fastest way to initiate therapy in hyperacute ischaemic stroke, but its efficacy in patients with LVO is questionable: it is well documented that IV TPA has limited efficacy in recanalising LVO [13-32] (see Table 2) and recanalisation is a strong predictor of good outcome [7,9,10,11,22-24,34]. The larger clot volume en-

Table 1 **Recanalisation is associated with a good clinical outcome. RECANALISE study, Mazighi et al. [11]. TIMI=Thrombolysis in Myocardial Infarction score used to assess degree of recanalisation (0=no recanalisation, 3=full recanalisation). mRS=modified Rankin Scale.**

Recanalisation	N	90 day good outcome (mRS 0-2)	Early neurological improvement
TIMI 0-1	7	0	14%
TIMI 2	9	22%	44%
TIMI 3	37	76%	73%
P		<0.001	0.006

Table 2 **Effect of IV TPA and occlusion site as measured using TCD. Saqqur et al. [22] CLOTBUST. NIHSS=National Institute for Health Stroke score; TIMI=Thrombolysis in Myocardial Infarction score. mRS=modified Rankin Scale.**

Occlusion	Proximal MCA	Distal MCA	ICA/MCA	TICA	BA	P
N	166	116	22	17	10	
NIHSS	18 (6-32)	13 (3-29)	19 (6-29)	20 (11-28)	27	
TIMI 3 <2h	30%	44%	27%	6%	35%	P=0.007
Early improvement	16%	33%	24%	0	25%	P=0.004
90 day mRS <1	25%	52%	21%	18%	25%	P<0.001
Mortality	24%	17%	14%	45%	75%	P=0.0024

sures a smaller surface area-to-volume ratio diminishing the effectiveness of IV TPA. Recanalisation results in only 4-18% of ICA occlusions and 22-32% of M1 occlusions using IV TPA [22-32]. Of those that do recanalise, recanalisation is often delayed and early re-occlusion is reported in approximately one third of IV TPA-treated patients [33]. The Calgary Stroke Programme [23] reported that of 127 patients receiving IV TPA that went on to have further imaging, only 27 (21.25%) patients had acute recanalisation (Table 3).

Table 3 **Recanalisation rates with IVTPA. TIMI=Thrombolysis in Myocardial Infarction score. Bhatia et al. [23].**

Occluded vessel	Recanalisation (TIMI 2 and 3)
M2 MCA	31%
M1 MCA	32%
TICA	4%
BA	4%

Having said this, clinical outcomes are improved with IV TPA in patients with CT angiographic evidence of proximal anterior circulation occlusions [6]. In the STOPstroke study, 35% of patients with NIHSS>10 treated with IV TPA achieved favourable outcome versus 17% of controls. Outcomes may, however, be less favourable in the context of greater thrombus loads or when the quality of collateral flow means that rapid recanalisation is required. IV TPA fails to recanalise occluded proximal vessels with thrombus longer than 8 mm assessed by thin slice non-contrast CT [17] and 70-84% of patients with a hyperdense MCA sign treated with IV TPA have a poor outcome (mRS 3-6) [18,19,20]. This may be why IV TPA has limited efficacy in those with clinically severe strokes. Twenty-eight per cent of stroke patients with an NIHSS score of 15-20 achieve a favourable outcome at one year when treated with IV TPA as compared to 21% of those receiving placebo [13]. In those patients with an NIHSS >20 treated with IV TPA, a favourable outcome was achieved in 6% compared to 4% treated with placebo [13]. In the IV TPA arm of the IMS 3 trial [12], 16.8% of patients with NIHSS >20 achieved a favourable outcome (mRS 0-2).

Table 4 **Results of studies comparing a combined intravenous (IV) and endovascular (EVT) approach with intravenous thrombolysis (IVT) alone. NIHSS=National Institute of Health Stroke Scale. SICH=Symptomatic Intracranial haemorrhage. mRs=modified Rankin Scale.**

Study	Technique		Presenting NIHSS		Outcome		SICH	
	IV+EVT	IVT	IV+EVT	IVT	IV+EVT	IVT	IV+EVT	IVT
Toyota et al [50]	0.6 mg/kg rtPA + IA rtPA micro-guidewire thrombus disruption, balloon angioplasty	0.6 mg/kg rtPA	17+/–2.8	16 +/–2.3 or +/–4.4	16/ 22 (72.7%) mRS 0-2	12/35 (34.9%) mRS 0-2	1/22 (4.5%)	2/35 (5.7)
Burns et al [51]	0.9 mg/kg rtPA + IA reteplase, Merci or snare devices or angioplasty.	0.9 mg/kg IV rtPA	15.8+/–3.5	16+/–3.5	11/33 33.3% NIHSS 0-2	4/30 (13.3%) NIHSS 0-2	4/33 (12.1%)	2/30 (6.7%)
Mazighi et al [11]	0.6 mg/kg rtPA + If arterial occlusion persisted, IA alteplase was given. If recanalisation did not occur after IV and IA alteplase, additional mechanical procedures were used (4 mm snare) or balloon angioplasty	0.9 mg/kg IV rtPA	16 (11-19)	14 (10-18)	30/53 (55%) mRS 0-2	47/107 (44%) mRS 0-2	5 (9%)	12 (11%)

Table 5 **Results of initial intravenous plus intra-arterial thrombolysis (IV+IA TPA) and early mechanical thrombectomy studies. NIHSS=National Institute of Health Stroke Scale. SICH=Symptomatic intracranial haemorrhage. TIMI=Thrombolysis in Myocardial Infarction. TICI=Thrombolysis in Cerebral Infarction score. mRS=modified Rankin Scale.**

	Control patients		**NINDS[21]**	**PROACTII[5]**	**IMS-I[43]**	**IMS-II[44]**	**MERCI[46]**	**Multi MERCI[47]**	**Merci registry[48]**	**Penumbra Pivotal Stroke Trial[52]**	**Penumbra POST[49]**
	NINDS (n=211)[73]	**PROACTII (n=59)[5]**	**IV TPA (n=182)**	**proUK (n=129)**	**IV/IA TPA (n=80)**	**IV/IA TPA±EKOS catheter (n=81)**	**Mechanical thrombectomy ± IA TPA (n = 141)**	**Mechanical thrombectomy ± IV TPA± IA TPA (n = 111)**	**Mechanical thrombectomy ± IV TPA± IA TPA (n =872)**	**n=125**	**n=157**
Mean age (SD), years	64 (10)	64 (14)	65 (11)	64 (14)	64 (13)	64 (12)	67 (16)	66 (17)	68 (median)	63.5 (13.5)	65 (15)
Median time to IV therapy, hours	1.8	NA	1.5	NA	2.3	2.3	NA	NA	NA	NA	NA
Mean/ Median time to endovascular therapy, hours	NA	5.1	NA	4.7	3.5	NA	4.3	4.2	6.3	4.3	4.5
Median NIHSSS	17	17	17	17	18	19	19	19	17	17.6	16
Recanalisation, % TIMI/ TICI 2/3	NA	18	NA	66	56	73	48	69	80.1	81.6	87
Recanalisation, % TIMI/ TICI 3	**NA**	**2**	**NA**	**19**	**11**	**4**	**24**	**NA**	**28**	**27.2**	**33**
90-day mortality %	24	27	21	25	16	16	44	34	33.4	32.8	20
SICH, %	1	2	6.6	10	6.3	9.9	7.8	9	7	11.2	6.4
90-day mRS ≤ 2, %	18	25	32	40	43	46	22.6	36	31.6	25	41

Endovascular therapy: IA TPA to mechanical thrombectomy

IA TPA alone: Intra-arterial delivery of TPA, directly into the thrombus (IA TPA) achieves a higher local concentration than IV TPA, theoretically allowing more complete recanalization with a lower dose of thrombolytic agent (Table 3). Recanalisation rates of 40-66% of M1/M2 occlusions [23,40-41] are achievable. The PROACT II study [5], a phase 3 randomised, multicentre, blinded follow-up trial, previously extensively referred to, demonstrated the effectiveness of IA thrombolysis with pro-Urokinase in patients with an MCA occlusion. Full recanalisation, Thrombolysis in Myocardial Infarction, (TIMI 3) was seen in 19% versus 2% of controls (both cohorts received heparin). Independent outcome was achieved in 40% of those treated with IA pro-Urokinase versus 25% of controls (p=0.043). SICH was 10% with pro-Urokinase versus 2% of controls. Ten day ICH and 90-day mortality were similar in both groups. Recently [42], subgroup analysis has shown that the chance of a favourable outcome with M2-MCA occlusions is doubled if treated with IA TPA.

In an observational study [41], consecutive patients with MCA occlusion exhibiting a hyperdense MCA sign on non-contrast CT, with similar NIHSS, were treated with IA TPA <6 hours or IV TPA <3 hours. A good outcome was achieved in 53% of IA TPA patients com-

pared to 23% of patients treated with IV TPA and mortality was lower with IA TPA (4.7% versus 23% for IV TPA). Seventy-one per cent of patients treated with IA TPA showed recanalisation.

IV plus IA TPA: Both Interventional Management of Stroke (IMS) 1 and 2 trials produced encouraging results when combining IV and IA thrombolysis. Favourable outcomes of mRS 0-2 were achieved in 43 and 46% respectively (see Table 5) [43,44], with partial or complete recanalisation achieved in 56-73% and SICH in 6-9.9% (in the NINDS [21] IV TPA arm, SICH was 6.6%). The study showed an advantage over age- and severity-matched controls from the IV TPA arm of the NINDS trial. A recent review suggests there is no difference in the rate of SICH following either full dose or three-quarter dose IV TPA followed by multimodal EVT [45].

First and second generation mechanical thrombectomy: Recanalisation rates are generally higher when mechanical thrombectomy is employed along with IA TPA [7,46-49]. Earlier techniques included microguidewire disruption or use of a snare or balloon angioplasty [11,50,51]. A summary of studies employing these techniques in addition to IV TPA is seen in Table 4. Subsequently, devices including the MERCI [46,47,48] (Concentric Medical Inc, Fremont, California, USA) and Penumbra aspiration catheter [49,52] (Penumbra Inc, Alameda, California, USA) were introduced (Table 5). Although the rate of recanalisation with distal perfusion (TIMI 3) was improved with the use of these devices it remained relatively low in the majority of these studies ranging from 24-33%. Fifty-six per cent achieved TICI 2b/3 recanalisation rates in the MERCI registry [48] but the time to treatment was relatively delayed (mean 6.3 hours) and a favourable outcome was therefore not improved - futile recanalisation. Time to recanalisation is crucial. Indeed, a favourable clinical outcome in many early thrombectomy studies was not superior to that seen in IV+IA TPA and in the IMS studies probably because the average time to EVT ranged from 4.2-6.3 hours (compared to 3.5 hours in IMS 1), negating the improved recanalisation rates.

Improved clinical outcome is achieved with shorter time to recanalisation [11,53] (Table 6). In the RECANALISE study, 93% of patients who recanalised in less than 210 minutes had a favourable outcome in comparison with those who recanalised later than 260 minutes, with a favourable outcome in only 37% [11] (Table 6). The probability of a favourable outcome decreases by approximately 20% for each 30-minute delay in recanalization [11]. In IMS III, a 30-minute delay led to a 10% decrease in the probability of a good outcome. Post hoc analysis suggested that faster recanalisation in the IMS III trial may have yielded a positive result [53].

A favourable outcome, for patients who undergo later treatment, is likely to result only in those with good collateral circulation. Collateral circulation is of vital importance and it is likely that perfusion imaging will help define the core infarct and salvageable parenchyma and may be particularly useful in those presenting later [54]. Discussion of patient selection based on these techniques, however, is beyond the scope of this review.

Recent trials

Three randomised controlled trials (RCTs) that have received much criticism [55] have recently been published: SYNTHESIS expansion [56], MR RESCUE [57] and IMS III [12]. Each is summarised (Table 7); all included currently outdated technology, predominantly IA TPA, microguidewire agitation, MERCI or Penumbra Aspiration devices.

The SYNTHESIS expansion trial [56] randomised patients to EVT or IV TPA. The IMS III trial [80] assessed the bridging approach, randomising to EVT or no EVT following initial treatment with IV TPA. The MR RESCUE trial [57] assessed the benefit of EVT over standard

Table 6 **Good outcome vs time to recanalisation; early recanalisation is associated with better clinical outcomes. RECANALISE, Mazighi et al. [11]. mRS=modified Rankin Scale.**

Time to recanalisation	Number of patients	90 day good outcome (mRS 0-2)	Early neurological improvement	P
>260 min	16	37%	37%	
210-260 min	15	67%	73%	0.07
<210 min	15	93%	93%	0.01

therapy but also stratified patients using MR diffusion-perfusion mismatch into those with presumed salvageable penumbra and those without.

SYNTHESIS Expansion [56]: This RCT of 362 patients randomized patients within 4.5 hours: half (181) received full dose IV TPA within 4.5 hours of ictus. The other half had attempted EVT within six hours of onset *without IV TPA*.

Key criticisms:

1) The site of occlusion was not documented and the trial was not confined to LVO (*no CTA was performed*). There was no lower limit for NIHSS (patients with NIHSS of as low as 2 were included). Approximately half in each arm had an NIHSS of <11. Therefore a large number of patients probably did not have LVO.

2) The median time to treatment was one hour later in the endovascular group (mean 2.5 vs 3.5 h).

3) Of the 181 patients assigned to EVT, 15 did not receive treatment. Most of the patients who were treated received locoregional infusion of TPA (median dose 40 mg (IQR 20-50 mg) and thrombus fragmentation with a microguidewire. IA TPA is generally accepted to have lower and slower recanalisation rates compared to stent-retrievers [60].

4) Only 23 endovascular patients had a stent-retriever deployed.

5) Extent of recanalisation by a grading scale (e.g. TICI) and time from onset to reperfusion was not reported.

Forty-two per cent of the EVT arm and a surprisingly high 46% of the IV TPA arm (which may reflect the relatively low number of true LVOs) achieved mRS 0-2 at three months. SICH was similar in both arms. The authors concluded that EVT (only IA TPA in most) was not superior to standard treatment. An alternative conclusion is that IA TPA, at approximately half the dose of IV, achieves equal clinical outcome when treating patients one hour later with a similar safety profile. This trial does not reflect modern management of hyperacute LVO.

Interventional Management of Stroke 3 [12]: This RCT of 656 patients in whom IV TPA was administered within three hours post ictus were randomly assigned to receive IV TPA alone (222 patients) or IV TPA followed by EVT (434 patients). The trial protocol evolved with time: initially, patients were included if NIHSS ≥10 but later, CTA was included in the protocol and patients with an NIHSS of 8 and 9 were enrolled if there was angiographic evidence of LVO. Thirty-three per cent only had CTA. Patients were randomised to EVT within 40 minutes of receiving IV TPA. Angiography began within five hours and was completed within seven hours after stroke onset.

Table 7 **Summary of the results of recent randomised trials. EVT=Endovascular therapy. IVT=Intravenous thrombolysis. mRS=modified Rankin Scale.**

Trial	Design	EVT	Median time to treatment	Mean time to recanalisation	Recanalisation rate (EVT)	Favourable outcome rate: (mRS 0-2)	Mortality
SYNTHESIS Expansion[56]	362 pts EVT: 181 IVT: 181	IA TPA 0.9 mg/kg to a maximum of 90 mg	EVT: 3.5 h IVT: 2.5 h	NA	NA	EVT: 42% IVT: 46%	EVT: 8% IVT: 6%
IMS III [12]	656 pts enrolled (target, 900) IVT+EVT: 434 IVT: 222	Treatment in 334 patients IA TPA only (n=266) MicroSonic SV system (n=22) MERCI (n=95) Penumbra (n=44) Solitaire (n=5) Other: (n=16)	IV+EVT: 249 min IVT: NA	NA	TICI 2b/3: TICA: 38% M1-MCA: 44% M2-MCA: 44% Multi M2-MCA: 23%	IV+EVT: 42.7% IVT: 49.2%	IV+EVT: 19.2% IVT: 21.6%
MR RESCUE[57]	127 pts (analysis restricted to 118) EVT: 57 (penumbral 34) Standard care: 70 (penumbral 34)	IA TPA: (n=8) (mean dose, 5.1 mg; range, 2 to 12 MERCI (NA) Penumbra (NA)	EVT: Mean: 6 h 21 min	NA	TICI 2/3: 65% TICI 2b/3: 25%	EVT (penumbral): 14% EVT (non-penumbral): 10% IVT penumbral: 23% IVT (non-penumbral): 10%	EVT (penumbral): 16% EVT (non-penumbral): 23% IVT penumbral: 9% IVT (non-penumbral): 22%

Key criticisms:

1) Most in the EVT arm received two thirds of the total dose of IV TPA and were therefore disadvantaged (especially if no EVT was then undertaken).

2) Only 334 patients of the 434 randomised to EVT (77%) received any intervention. In the 89 who did not receive treatment, the investigator did not identify a suitable target in most - either no LVO or distal inaccessible thrombus.

3) The majority were treated with either IA TPA only, or older devices including MERCI (57 pts) and Penumbra (38 pts). Only five patients were treated with stent-retrievers - this trial also does not reflect modern practice.

4) Satisfactory recanalisation (TICI 2b/3) rates were low, ranging from 23% for multiple M2 occlusions to 44% for M1 or isolated M2 occlusions and this may account for the disappointing results in the endovascular arm. There are no data on time to recanalisation.

5) Of the IV TPA arm, the recanalisation rates were assessed in a minority and at 24 hours; this is likely to overestimate effective reperfusion.

6) Occlusion site were recorded in the EVT arm (TICA 100, M1-MCA 167, M2-MCA 87, multiple M2-MCA 22 patients). In the IV TPA arm, CTA data on admission was available in only 95 patients and at follow-up in only 69.

7) The study concluded that there is little benefit in attempting recanalisation with older generation endovascular approaches beyond the 4.5 hour window in the majority of patients: overall favourable outcome (mRS 0-2) was 42.7% for the EVT group and 49.2% for the IV group.

However, post hoc analysis [58] of those patients with a CTA on admission demonstrated that there was significant improvement in outcome (45% vs 38%, P=0.0114) for those with a proven LVO on CTA in the EVT cohort. This difference was greatest for terminal ICA occlusions. Favourable outcomes for those with an NIHSS >20 tended to significance (p=0.06) in favour of EVT (23.8% for EVT vs 16.8% for IVT). There were no safety concerns and the SICH rate was similar (6.2 vs 5.9%) as was mortality at 90 days (19.2 vs 21.6%).

MR RESCUE [57]: In this trial of 118 patients, 70 were randomised to receive EVT and 58 to standard therapy in 22 USA centres, over six years during which device technology changed. Patients were stratified based on having a favourable or unfavourable penumbral pattern. The former was defined as a predicted infarct core of 90 ml at most and the at risk tissue 70% or less. Forty-four (37%) received IV TPA prior to randomisation (16 (47%) and 12 (40%) of the penumbral and non-penumbral embolectomy patients respectively and nine (26%) and seven (35%) of the respective penumbral and non penumbral standard care patients). In the embolectomy arm, 34 with a favourable pattern and 30 with a non penumbral pattern underwent EVT.

Key criticisms:

1) The study had very slow recruitment over a long time period over which technology evolved. Either the MERCI Retriever (since trial initiation in 2004) or the Penumbra System (since 2009) were employed. Adjunctive IA TPA was administered in eight patients at a dose of 5.1 mg; range, 2-12 mg.

2) The mean time to enrolment in the study was 5.5 hours.

3) Although 64% achieved TICI 2/3 recanalisation overall, only 25% (16 patients) in the endovascular arm achieved TICI 2b/3 recanalisation [NEJM supplementary data]. Therefore, testing the hypothesis that penumbral imaging would identify patients who would benefit from EVT within eight hours of symptom onset was impossible. In contrast, DEFUSE II, a multicentre prospective study [59] concluded that there was a significant benefit from recanalization in patients receiving EVT (recanalization rate 46% TICI 2b/3) with a favourable penumbral pattern.

Modern thrombectomy: stent-retrievers

Currently, clot extraction is usually achieved using stent-retrievers. These consistently restore flow on deployment prior to thrombus extraction. Flow restoration is faster than other methods and procedural times are significantly shorter [60].

A systematic review of published series using the Solitaire device (ev3 Neurovascular, Irvine, California, USA) demonstrated a recanalisation rate of 89.7% and a favourable outcome (mRS 0-2) in 47.2% of 262 patients [61]. Multiple series have subsequently been published [62-77] (see Table 8 for series of at least 30 patients). Independent outcomes (mRS 0-2 at 90 days) are now reported in approximately 55% (42.5-77%) [60-77] in those with LVO with moderate/severe strokes. This relatively wide range likely reflects

Table 8 **A summary of series using stent-retriever technology in acute stroke. NIHSS = National Institute of Health Stroke Scale. SICH = Symptomatic intracranial haemorrhage. TIMI = Thrombolysis in Myocardial Infarction Score. TICI = Thrombolysis in Cerebral Infarction score. mRS = modified Rankin Scale.**

Study/Device	No patients	Mean/Median NIHSS (range or SD*)	Recanalisation Rate	Outcome	Mortality	SICH
Machi et al.[62] Solitaire	56	16 (7-26)	TICI≥2b: 89.3%	mRS≤2 at discharge: 47%	7.14%	1%
Davalos et al.[63] Solitaire	141	18 (1-32)	TICI≥2b: 85%	mRS ≤2 at 90 days: 55%	20%	4%
Koh et al.[61] (Solitaire; systematic review)	262	14-21 (4-21)	TIMI 2-3 or TICI≥2b: 89.7%	mRS≤2: 47.2%	11.1%	6.8%
Dorn et al.[65] Solitaire	104	15.3 (2-27)	TICI≥2b: 79% (anterior); 77.9% (posterior)	Mean NIHSS reduction at discharge 7.8	Anterior: 15.5% Posterior: 47.8%	1.9%
Broussalis et al.[66] Solitaire/Trevo	62	17 (6-26)	TICI≥2b: 82%	mRS≤2 at 90 days: 36/61 (59%)	8%	10%
San Roman et al.[67] Trevo	60	18 (12-22)	TICI≥2b: 86%	mRS≤2: 45%	28%	12%
Pereira et al.[68] Solitaire (STAR Study)	202 pts 14 centres	17	TICI≥2a: 94.7%	mRS≤2: 57.9%	6.9%	1.5%
Mokin et al.[69] Solitaire	101	17.6 (6.4*)	TIMI 2/3: 88%	(mRS ≤2 or NIHSS score improvement by ≥10 points or return to pre-stroke mRS score: 47%	26%	15%
Cohen et al.[70] Solitaire	33	19.5 (4.3*)	TIMI 3: 94%	mRS 0-2 at 90 days: 77%	10%	3%
Tuilier et al.[71] Solitaire	36	16 (7-24).	TICI≥2b: 89%	mRS 0-2 at 90 days: 58.5%	19.5%	0
Costalat et al.[72] Solitaire (RECOST study)	50	15 (3-23)	TICI≥2b: 88%	mRS 0-2 at 90 days: 54%	12%	2%
Prothmann et al.[73] Phenox	54	16.6	TICI≥2b: 61.9% TIMI 2/3:85.5%	NIHSS improvement at discharge: 54%	30.4%	5.5%
Roth et al. Solitaire[74]	40	16.4 (4.1*)	TICI≥2b: 95%	mRS 0-2 at 90 days: 60%	12.5%	1.7%
Bae et al.[75] Solitaire	40	14.1 (8-26)	TICI≥ 2a: 90% TICI 3: 37.5%	mRS 0-2 at 90 days: 42.5%	5%	2.5%
Soize et al.[76] Solitaire	59	17.7(6.2*)	TICI≥2a: 83%	mRS 0-2 at 3 months: 57.9%	20.4%	8.5%
Ribo et al.[60] Solitaire/TTrevo	69	18 (17-20)	TICI≥2b: 68.7%	mRS 0-2 at 3 months: 52.8%	NA	10.8%
Raoult et al.[77] Solitaire	45	17 (6-32)	TICI≥2b:93%	mRS 0-2 at 3 months: 58%	18%	7%

the differing characteristics of cohorts in terms of site of occlusion, core infarct at presentation, collateral status and timing of intervention but the general trend to more superior clinical outcomes compared to earlier studies (table 5) may well be secondary to improved recanalisation. Some series report rates of recanalisation with Solitaire in excess of 95% [78,79]. Encouraging results have also been achieved with the Revive device (Codman Neurovascular, DePuy Synthes New Brunswick, New Jersey, USA); in ten patients, TICI 2b/3 was achieved in 100% [80]. Other stent-retrievers include the Phenox clot retriever [73] (Phenox GmbH, Bochum, Germany), Aperio (ACANDIS GmbH & Co, Pforzheim, Germany), the Penumbra 3D (Penumbra Inc, Alameda, California, USA) and the Trevo device [66,67] (Concentric Medical Inc, now Stryker, Fremont, California, USA).

Recently, the results of the STAR trial [68] were published. This was a single arm prospective international, multicentre study of thrombectomy using the Solitaire device in patients with large vessel anterior circulation strokes treated within eight hours of symptom onset at 14 centres. Two hundred and two patients with a mean NIHSS of 16.5 and occlusion sites including TICA (18%), M1-MCA (67%), M2-MCA (14%) were treated. Overall recanalization rate (TICI ≥2b) was 79.2% with a favourable clinical outcome (mRS 0-2) in 57.9%. Mortality was 6.9% and SICH rate was very low at 1.5%.

Stent-retrievers vs older devices: Several studies have confirmed the superiority of stent-retrievers over the outdated technology used in the recently reported trials [60,64,66,81]. Compared to IA TPA or the MERCI device, the rate of complete recanalization is higher, time from groin puncture to initial flow restoration and final recanalisation is shorter and the favourable outcome (mRS 0-2) rate is higher [60,66].

The SWIFT study [64], a multicentre RCT recently demonstrated that the Solitaire stent-retriever was superior to MERCI for recanalisation, less SICH, reduced mortality and improved favourable outcomes. TICI 2b/3 recanalisation was seen in 61% of the Solitaire group vs 24% of the MERCI group. More patients had a good three-month neurological outcome (mRS 0-3) with Solitaire than with MERCI (58% vs 33%). This study was halted prematurely due to the significantly higher mortality rate in the MERCI arm (38.2 vs 17.2, p=0.02).

The Trevo stent-retriever also has a proven benefit over the MERCI device [81]. TICI 2/3 recanalisation was seen in 86% of the Trevo group vs 60% of the MERCI group. More patients had good three-month neurological outcome (mRS 0-3) with Trevo than with MERCI (55% vs 40%). SICH occurred in 6.8% in the Trevo group and in 8.9% of the MERCI group with mortality rates of 33% versus 24% respectively.

Bridging to stent-retriever thrombectomy: Immediate IV TPA prior to stent-retriever clot extraction in patients with LVO and moderate/severe strokes is theoretically useful. This serves as a bridging mechanism until the angiography suite is ready and/or patient transferred in from an outside institution for urgent thrombectomy. There is some evidence that patients treated with both mechanical thrombectomy and IV TPA have better outcomes than those treated with EVT alone. In 141 stent-based clot extractions, the rate and degree of neurological recovery (NIHSS 0–1), 24 hours post procedure up to three months, was significantly higher in patients initially treated with IV TPA than in those without (favourable outcomes: IV TPA, 66%; no IV TPA, 42%; $P<0.01$) [63]. Although it has been suggested that pre-treatment with IV TPA may soften the thrombus, favouring catheter penetration and retrieval, the results of the STAR trial suggest that there is no significant difference in the recanalization rate between those treated initially with IV TPA versus those without [68], so perhaps a second mechanism is at play. The standard of care full dose IV TPA is considered safe prior to EVT [45].

Rescue stent-retriever thrombectomy: Several studies have demonstrated superior outcomes in patients treated with EVT after a failure to respond to IV TPA [82-85]. A recent single centre study assessed stent-retriever EVT following clinical failure of IV TPA [82]. At three months, 17/22 (77%) patients from the EVT and 15/30 (50%) from the IVT group achieved an mRS score of 0-2. The high percentage of good outcomes might relate to the fact that DSA was commenced prior to completion of IV TPA and the mean time from ictus to recanalisation was still under five hours. Thrombectomy was strongly associated with favourable clinical outcome ($P < 0.02$). Delayed EVT did not increase SICH. The recanalisation rate was much higher than IMS 3 [12] and MR Rescue [57] with TICI 3 in 88%.

Isolated mechanical thrombectomy with stent-retriever vs standard therapy: Lecker et al. [86] compared consecutive patients with M1 occlusions treated with stent-retriever-based throm-

bectomy (22 patients) with 66 treated with IV TPA. The thrombectomy patients had higher admission NIHSS scores (median 21 vs 14.5; *P*<0.001) and prolonged symptom onset-to-treatment times (median 240 vs 95 minutes; *P*<0.001). At discharge, the magnitude of change in NIHSS was larger in the thrombectomy group (median 12 vs 6 points; *P*<0.001). At 90 days post ictus there was a significantly improved rate of favourable outcome in the thrombectomy group (60% vs 37.5%; p=0.001).

Complication rates: The rate of SICH in patients treated with IV TPA in the NINDS trial [87] was 6.6%, 8.8% in the ECASS II study [88] and 7.2% in the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke study [89]. A meta-analysis of 27 studies demonstrated a rate of 8% (95% CI, 6-10) for SICH after EVT [90]. These rates are similar to the majority of patients in IV TPA trials, who have small vessel occlusions. The SICH rate in patients receiving IV thrombolytic therapy specifically for LVO with a dense MCA sign on non-contrast CT is 11% [91]. A recent meta-analysis demonstrated that the SICH rate for TICA occlusions when treated with IV TPA was 23% but only 9.9% for EVT [8]. Using stent-retrieval with the Solitaire device, rates of SICH on systematic review have been shown to be 6.8% [61]. Our review of the recent stent-retriever literature suggests that this ranges from 1.5-15%.

Conclusions

The natural history of LVO is poor and there is little evidence for the efficacy of IV TPA. The recently reported trials used delayed and less effective means of recanalisation and do not reflect modern practice. Timely effective recanalization is associated with a favourable outcome in moderate/severe strokes with LVO. EVT using stent-retrievers efficiently and effectively achieves LVO recanalisation, either alone or in combination with IV TPA. If performed early post ictus, outcomes may be favourable, often in more than 50% of patients. The rate of SICH following mechanical thrombectomy using stent retrievers is similar to that reported for IV TPA suggesting that mechanical thrombectomy is a safe as well as effective method of recanalisation.

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